

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%

**Full Safety and Drug Utilization Review
Provided in Background Materials**

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Background Labeling

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% & 10%

- An alpha-1 adrenergic receptor agonist indicated to dilate the pupil.
- Marketed for over 70 years; however first approved under an NDA in 2013, which triggers this review.
- The support of efficacy is based on previously published studies, including 2 special safety studies, one of premature neonates (Sindel) and one of neonates <1 mo of age (Borromeo-McGrail).

References

Sindel BD et al. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. J Pediatr Ophthalmol Strabismus 1986.

Borromeo-McGrail V et al. Systemic hypertension following ocular administration of 10 per cent ² phenylephrine in the neonate. Pediatrics 1973.

Phenylephrine Hydrochloride Ophthalmic Solution Labeling

Dosage and Administration

- For patients ≥ 1 year of age, apply 1 drop of 2.5% or 10% solution at 3 to 5 minute intervals with a maximum of 3 drops per eye.
- For pediatric patients < 1 year of age, 1 drop of 2.5% should be instilled at 3 to 5 minute intervals up to a maximum of 3 drops per eye.

Contraindications

- Phenylephrine Hydrochloride Ophthalmic Solution, 10% is contraindicated in pediatric patients < 1 year due to increased risk of systemic toxicity.

Phenylephrine Hydrochloride Ophthalmic Solution Labeling

Warning and Precautions

- Reports of serious cardiovascular reactions, some fatal, with phenylephrine hydrochloride 10% solution. Monitor blood pressure in patients with cardiovascular disease.
- Significant elevations in blood pressure have been reported. Caution in pediatric patients <5 years of age, and in patients with elevated blood pressure.

Systemic Adverse Reactions

- A marked increase in blood pressure has been reported particularly, but not limited to low weight premature neonates, infants and hypertensive patients.
- Cardiovascular reactions which have occurred primarily in hypertensive patients following topical ocular use of the phenylephrine hydrochloride ophthalmic solution 10% included marked increase in blood pressure, syncope, myocardial infarction, tachycardia, arrhythmia and subarachnoid hemorrhage.

Phenylephrine Hydrochloride Ophthalmic Solution Labeling

Pharmacodynamics

- Maximal mydriasis occurs in 20 to 90 minutes with recovery after 3 to 8 hours.
- Systemic absorption of sufficient quantities of phenylephrine may lead to systemic α -adrenergic effects, such as rise in blood pressure which may be accompanied by a reflex atropine-sensitive bradycardia.

Pharmacokinetics

- The systemic exposure following topical administration of phenylephrine hydrochloride ophthalmic solution has not been studied.

Pediatric Post-market Review

Non-fatal, nonUS SAEs; n=3 literature case reports

- A 3-month-old girl born 28 weeks gestation had a myclonic seizure after receiving cyclopentolate and phenylephrine for ROP* screening. There was a positive rechallenge 4 days later. Authors attributed the event to cyclopentolate.
(Cyclopentolate is labeled for seizures).
- A 6-year-old boy with generalized tonic-clonic seizures on two separate occasions 1 year apart after ocular instillation of cyclopentolate, proparacaine, tropicamide, and phenylephrine eye drops. Authors attributed the strongest association of the events to cyclopentolate.

***ROP retinopathy of prematurity**

Pediatric Non-fatal nonUS SAEs (continued)

- A 9-day-old female with congenital bilateral cataract with bilateral granulomatous uveitis, treated with prednisolone hourly, phenylephrine 5% and atropine 0.5% twice daily without effect (drug ineffective).

Pediatric Postmarket Review

NonUS Fatal SAE – 1 literature case

A neonate born 26 weeks gestation weighing 1050 gms received slow enteral feedings until 33 days of age due to intermittent gastric retentions. She had ROP screening, age 37 days. Enteral feeding stopped 2 hours before eye exam with 2 doses of cyclopentolate 0.5% and phenylephrine 1.25% eye drops diluted two-fold. Approximately 4 hours after, she developed "cutis marmorata" (livedo reticularis) and tachycardia associated with "abdominal distension." She was intubated and put on mechanical ventilation. She developed leukopenia and neutropenia, platelets normal. At 12 hours after exam she was diagnosed with "stage III - diffuse necrotizing enterocolitis"(NEC), and then died 24 hours after bowel resection. Authors emphasized the serious side effects of these mydriatic drugs.₈

Phenylephrine Hydrochloride Ophthalmic Solution, Pediatric (0-16 years) Drug Utilization

- **Outpatient Non-retail Pharmacy Settings, 3/2013-2/2015***
 - Approximately 317 of 5,155 (5.4%) prescription claims were for pediatric patients aged 0-16 with the largest proportion in the 2-11 year old age group.
- **Inpatient drug utilization data was unavailable.**

*Source: Symphony Health Solutions' Integrated Dataverse (IDV). March 2013-February 2015. Extracted May 2015.

Retinopathy of Prematurity (ROP) Screening Exams

- Frequently performed, they are important for early detection and treatment of ROP which can prevent detachment of retina and resulting blindness.
- ROP screenings are routinely performed in NICUs.
- Especially important for preterm infants ≤ 30 weeks, and < 1500 gms, with exams performed every 1 to 3 weeks.
- ROP exams may be painful and stressful for the infant.
- Oculocardiac reflex during the exam may cause apnea and bradycardia.
- Ophthalmic eye drops that have anticholinergic and α -adrenergic properties may be absorbed with systemic effects.

References

Mitchell AJ et al. Physiologic effects of ROP screening examinations. Adv Neonatal Care. 2011.
Policy Statement-Screening examination of premature infants for ROP. Pediatrics 2006.

Summary

- **NEC is a common disease in premature infants.**
- **While it is plausible that ROP screening with the application of phenylephrine and cyclopentolate mydriatic eye drops may have possibly contributed to the death of the premature infant, other factors were likely involved.**
- **The 2 non-fatal SAEs with seizures were most likely due to cyclopentolate.**

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FDA plans to continue its standard ongoing safety monitoring.

Does the Committee concur?

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Back up slides

Phenylephrine Hydrochloride Ophthalmic Solution, Outpatient Pediatric (0-16 years) Drug Utilization

March 2013 - February 2015		
	Patient Count N	Share %
Phenylephrine Ophthalmic Total Patients	5,924	100.0%
0-16 years	317	5.4%
0 - 1 years	19	6.0%
2 - 11 years	248	78.2%
12-16 years	50	15.8%
17+ years	5,606	94.6%
Unspecified age	1	<1%

* Claims are from U.S. commercial, Medicare Part D, Cash, and Medicaid plans. Data includes patients with prescription claims.

Note: age is at first claim during examined time period. Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).

Source: Symphony Health Solutions' Integrated Dataverse (IDV). March 2013 - February 2015. Extracted May 2015. File: SHSCPA 2015-359 phenylephrine ophthalmic results May-2015.xls

*Data represent sample of 4,329 specialty pharmacies, clinics, hospitals and physician offices